II. NICOTINE PHARMACOKINETICS

Tobacco leaves have a nicotine content between 0.2% and 5% of the dry weight. In a cigarette there is about 10 to 20 mg of nicotine and 14 to 20% is transferred into the mainstream smoke so a 35 ml puff on a 1.2 mg cigarette will give a mouth level of 150-250 µg of nicotine (Armitage, 1973). Tobacco smoke has about 2000 other compounds in it as a complex mixture of gases, uncondensed compounds and liquid droplets as an aerosol. The pH of the mainstream smoke ranges between 5.5 and 6.2 for flue cured cigarettes and between 6.5 and 8.8 for cigar and pipe smoke. The level of acidity is crucial in determining the site of absorption and the amount of nicotine taken from the aerosol.

A. Absorption

The first requirement for a chemical to produce a biological response is absorption. Nicotine from tobacco smoke is absorbed from the mouth, nose, and lungs and digestive tract and the amount absorbed from most sites depends on the acidity of the total smoke.

1. Oral Absorption

Nicotine base is readily absorbed by the buccal membrane from the particulate phase of smoke but, as the amount of free base depends on pH, the amount of nicotine absorbed orally depends on pH. When the pH is 5.35, about 0.4 per cent of the nicotine is present as the free base, while at pH 8.5 (alkaline), 85 per cent of the nicotine is present as the free base. Beckett and Triggs (1967) found in humans that from 1.2 mg of nicotine base about 6% was taken up at pH 5.5 and 25% at pH 8.5. Animal studies with nicotine solutions have shown that a carotid nicotine level of 100 ng/ml can be achieved at pH 6 in the mouth but this increases to 500 ng/ml at pH 8 (Armitage and Turner, 1970). Unpublished research by Dr M A H Russell and Dr K Wesnes, showed that buccal absorption from alkaline tablets containing 1.5 mg nicotine gave venous levels of 6.0 ng/ml at pH 6 and 10.5 ng/ml at pH 9. From these data it would be expected that very little nicotine

would be absorbed orally from cigarette smoke (pH 5.5 to 6.2), perhaps as little as 30% (Armitage, 1973), although much more is taken up from cigar smoke (pH 6.5 to 8.8). In a bioassay study to compare oral absorption of cigar and cigarette smoke, Armitage and Turner (1970) introduced equal numbers of puffs of cigar smoke at pH 8.5 and of cigarette smoke at pH 5.4 into the mouth of an anaesthetised cat. The cigar smoke produced an increase in blood pressure in the femoral artery but cigarette smoke did not. In the same study the oral uptake of radioactively labelled nicotine was compared at pH 7 and pH 8, there was much more taken up when the pH was 8. Thus oral absorption appears to be important for cigar and pipe smokers but much less significant for cigarette smokers. Consequently, a crucial part of the cigarette smoking habit is the further manipulation of smoke by inhaling and then expelling through the nose and mouth or even just expelling through the nose.

2. Nasal Absorption

In order to account for the habit of snuff taking, which is found in many cultures, and the popularity of snuff taking among smokers working in munitions factories, it has been suggested that nicotine is absorbed by the nasal mucosa (Proosdij, 1960). Evidence for this explanation has come from two studies. Temple (1976) found that snuff taking resulted in measurable levels of nicotine and its major metabolites in urine. More recently, Russell described the time course of plasma nicotine that resulted from snuff taking by an experienced snuff taker (Russell, Jarvis and Feyerabend, 1980). Uptake of nicotine from the nasal mucous membrane was extremely rapid and nicotine concentrations of over 20 ng/ml were found in blood samples from a forearm vein. Therefore, it would seem probable that nicotine is absorbed from the nose during smoke manipulation but the absorbed amount is probably small in comparison with the uptake that results from inhalation.

3. Inhalation

The major site of nicotine absorption for cigarette smoke (and so for the majority of smokers) is the lungs. During inhalation, the smoke

aerosol passes down the bronchi and into the alveoli. Particles of cigarette smoke are an ideal size (0.01 - 2 µm) for penetration into the alveoli and absorption occurs through the thin alveolar membrane into the pulmonary capillaries. It is estimated that more than 90% - 95% of inhaled nicotine is absorbed (Armitage, Dollery, George, Houseman, Lewis and Turner, 1974; Armitage and Turner, 1980; Artho and Grob, 1964). When equivalent sized boli of cigar or cigarette smoke were puffed into a cat's lung, changes in femoral artery blood pressure suggested much more efficient uptake of nicotine from cigarette smoke than cigar smoke (Armitage, Hall and Morrison, 1968). Nicotine diffuses so rapidly across the alveolar membrane and the velocity of blood flow through the capillaries is so slow that equilibrium is probably reached between alveolar nicotine and capillary nicotine ensuring maximum uptake. On the basis of the previous estimates of 150 to 250 µg mouth level of nicotine from each puff, over 100 µg would be taken up during each inhalation from a medium delivery cigarette (Armitage, Houseman, Turner and Wilson, 1974) giving over 1.0 mg of nicotine per cigarette. Of course, the actual intake may not only depend on smoke generation (puffing pattern) and smoke manipulation (quantity inhaled and depth of inhalation) but also perhaps on smoke moisture, pH of mucus membrane, and the contact time with the alveoli.

The time course of nicotine in human plasma has been studied most extensively by Dr M A H Russell. Smokers puffed ten times on a cigarette and plasma samples were taken every five minutes from an indwelling needle in a forearm vein. There was a rapid increase in plasma nicotine with each puff with irregularities in the ascent profile from the puff by puff boluses of nicotine. Peak venous nicotine levels of 15.5 to 38.4 ng/ml were reached at the end of the cigarette and then corresponded to about one fifth or one sixth of the carotid artery levels. Nicotine decay is not smooth either, and Russell (1976) argues that the irregularities represent nicotine redistribution and recycling. The estimated overall half-life in humans is around 20 mins after finishing the cigarette and baseline levels of about 7 ng/ml are reached in 40 mins.

4. Gastric Absorption

Gastric absorption only plays a small part in nicotine uptake from cigarette smoking in normal circumstances. Nicotine from the smoke aerosol will dissolve in the saliva where pH ranges of between 5.6 and 7.6 would give about 6 per cent to 20 per cent free nicotine base. Travell (1967) showed that nicotine was rapidly absorbed from a cat's stomach when the solution pH was between 7.8 and 8.6 but not when the solution was acidic, with a pH between 1.2 and 4.2. There is evidence of active nicotine excretion from the salivary glands. This nicotine passes into the stomach and Russell (1976) has suggested that this "recycled" nicotine could maintain the plasma levels of nicotine in smokers. However this seems unlikely; the normal gastric pH is acidic and so nicotine will be absorbed very little from the stomach although absorption from other regions of the digestive tract cannot be ruled out.

5. Summary

The amazing, complicated practice of puffing on burning tobacco leaves, inhaling the smoke and blowing it out through the nose and mouth has a simple explanation. This procedure enables the most efficient transfer of nicotine from the tobacco leaves to the smoker's bloodstream and more importantly the smoker can control the level of nicotine intake (see Section III).

B. Distribution

After absorption into the pulmonary capillaries, nicotine does not bind to plasma protein and so all the nicotine is available for biological activity. The nicotine-loaded blood leaves the lungs via the pulmonary veins and passes through the left atrium of the heart into the left ventricles. From there the nicotine is pumped out into the aorta from which the large arteries branch off. The significant branch, from the point of view of the smoking habit, is the carotid artery which leads directly to the brain, so that some absorbed nicotine passes directly unmetabolised from lung to brain within 10 secs. About a fifth of the blood from the heart ascends in the carotid artery so that a fifth of the absorbed nicotine passes to the brain (Oldendorf, 1977) ie a dose of around 250 µg from a medium delivery cigarette on the basis of the previous assumptions.

1. Brain

In order to act on the brain, a substance must penetrate the blood-brain barrier (mainly the membrane lipid of the brain capillary walls) to the brain extracellular fluid. Nicotine is soluble in lipid (partition coefficient of 0.4) which suggests that it will freely pass through this barrier. Studies in the rat have compared the percentage of nicotine remaining in the brain 15 seconds after a rapid intracarotid injection with tritiated water as a standard. Ninety per cent of the tritiated water is taken up by the brain on the first pass through the brain, and uptake of nicotine is 131% that of tritiated water. (Oldendorf, Hyman, Brown and Oldendorf, 1972). Thus virtually all the nicotine that is delivered to the brain leaves the blood since the volume of brain tissue to which it can distributed is so much larger than the capillary plasma volume. As a result, the amount of nicotine entering the brain is proportional to the cardiac output to the brain ie about 250 µg nicotine per cigarette. As a consequence of this efficient uptake of nicotine, doses affecting the brain can be obtained with relatively low blood levels which minimises the risk of toxicity to other organs in the body.

Whole body autoradiograms of mice given intravenous doses of ^{14}C-nicotine reveal a high accumulation of nicotine in the grey matter (unmyelinated tissue) with much smaller quantities in the white matter. This distribution occurs because nicotine's partition coefficient of 0.4 allows good penetration of the blood-brain barrier but does not result in depot fat storage. Microautoradiograms after ^{14}C-nicotine and ^{3}H-nicotine show radioactivity in cortical cells, high levels in molecular and pyramidal cells of the hippocampus, the molecular layer of the cerebellum, the nuclei of the hypothalamus and the brain stem (Schmiterlöw, Hanson, Applegren and Hoffman, 1967). This pattern of nicotine distribution throughout the brain allows wide scope for pharmacodynamic interaction.

The time course of nicotine distribution in mouse brain shows that the maximum concentration is reached within one minute of an intravenous injection. The level then decreases rapidly to about 50 per cent in five minutes and one per cent after an hour (Stalhandske, 1970). Similarly Schmiterlöw found a rapid nicotine decrease from 3.93 µg (per gram of brain tissue) at five minutes to 0.71 µg at 20 minutes and 0.10 µg at one hour (Schmiterlöw, Hanson and Andersson, 1967). As these workers and others found, the brain does not metabolize nicotine but the drug washes out quickly from the brain and so gives a short duration of action. Thus nicotine is a drug which is rapidly absorbed into the brain, widely distributed and then quickly removed; the ideal specifications for a substance that is required for a short duration of action.

2. Rest of the Body

The nicotine that is eliminated from the brain is redistributed around the rest of the body and joins the nicotine introduced via the other arteries from the aorta. As the partition coefficient is less than one very little storage in solution in fatty tissues results. Instead, whole body autoradiograms (Schmiterlöw et al 1967) show a pattern of distribution after intravenous injection that corresponds to the blood supply, with the highest levels of radioactivity in the liver (4% of the injected dose), about the same levels in the kidneys as in the brain (2% of the injected dose) and less in the stomach.

In contrast to the brain, nicotine is metabolised in the liver and kidneys (see next section) and nicotine levels in the liver fall from 8.12 µg (per gram of tissue) at five minutes to 0.76 µg at 20 minutes ie about 90% is metabolised in 15 minutes. At 20 minutes the radioactivity in the liver and kidneys is mainly due to cotinine and other metabolites of nicotine (Schmiterlöw et al 1967).

C. Metabolism and Excretion

Metabolism and excretion have been discussed at length in numerous publications. However there are two aspects of major importance to the smoking habit. First, it is clear from the time course that nicotine

is metabolised very efficiently by the liver, this limits nicotine's duration of action in the body. Second, the metabolites appear to be virtually inactive. Metabolic transformation is carried out by the enzyme systems of the liver microsomes and it seems that microsomal oxidation systems are protected by a lipoid barrier (Brodie, Maickel and Jondorf, 1958) which nicotine is fat-soluble enough to penetrate. The major metabolic route is probably hydroxylation (insertion of a carbonyl group in the pyrrolidine ring) to form cotinine. In addition, other metabolites, including nicotine 1-N-oxide and nornicotine, are formed and excreted. The importance of this metabolic outcome is that no compounds of demonstrated pharmacological action are produced and the pharmacodynamic effects are determined almost completely by the action of nicotine alone.

D. Conclusion

Studies of nicotine pharmacokinetics have revealed it to be a substance which is absorbed very efficiently from the lungs, readily enters and is quickly eliminated from the brain, and is rapidly metabolised to relatively inactive metabolites. This pharmacokinetic pattern allows a brief duration of action and the possibility of central nervous action with minimum side effects from actions on the rest of the body. The realization of this possibility depends on the ability of the smoker to control his exposure to nicotine ie titrate for nicotine.